

EXHIBIT A



Osteoporosis Diagnosis

En Español

How Diagnosis of Osteoporosis Is Done

The gold standard for diagnosis of **osteoporosis** is dual energy x-ray absorption scan (DEXA scan). The test is performed by passing low energy x-rays through a bone (e.g. spine, hip or wrist). The test takes about ten minutes, is painless, and is associated with very limited radiation exposure. The values generated by the test can then be compared to both:

- *Young adult population*—called a "T score", this test measures the variance between the patient and the young adult baseline. A score above -1 is considered normal; a score between -1 and -2.5 is considered osteopenia; and a score below -2.5 is considered osteoporosis. For each -1 standard deviation in T score there is a 3 times increased risk of hip fracture and a 2.5 times risk of spine fracture.
- *Age- and gender-matched control groups*—a "Z score" measures the variance between the patient's and control groups' amount of bone. The control group consists of other people in the patient's age group of the same size and gender. An unusually high or low score may indicate the need for additional tests.

Using statistical analysis, the DEXA scan diagnostic study can indicate if someone is at increased risk of sustaining a fracture. According to the National Osteoporosis Foundation, bone mineral density testing is recommended in the following situations:

- All women over age 65
- Postmenopausal women under age 65 who have multiple risk factors
- At menopause, if undecided about hormone replacement therapy
- Abnormal spine x-rays
- Long-term oral steroid use
- Hyperparathyroidism (over-active parathyroid gland)

An osteoporosis diagnosis distinguishes whether or not osteoporosis is a primary problem or is secondary to another problem. Therefore, a thorough history and physical examination, as well as the appropriate diagnostic tests, need to be obtained. It is important to distinguish primary from secondary because the treatments are often different.

Common causes of secondary osteoporosis include:

- *Endocrine disorders* (hypogonadism, Cushings disease, hyperthyroidism, hyperparathyroidism, diabetes mellitus)
- *Marrow disorders* (multiple myeloma, disseminated cancer, chronic alcohol use, lymphoma)
- *Collagen disorders* (osteogenesis imperfecta, Marfans syndrome)
- *Gastrointestinal disorders* (Malabsorption, malnutrition)
- *Medications* (Aluminum antacids, anti-convulsants, chemotherapy, glucocorticoid therapy, thyroid hormone replacement)

By: Donald J. Frisco, MD

June 21, 2006 (Originally published November 1999)

Osteoporosis Pictures
Find Top Information, Facts, And
Pictures On Osteoporosis Now.
OsteoporosisFacts.net

Osteoporosis scores
Relax. Take a deep breath. We
have the answers you seek.
www.righthealth.com/Osteoporosis

Osteoporosis - Bone Loss
Bone Loss is Curable. Get the
Facts.
GreatHealthResource.info/Osteoporosis

Osteoporosis treatment
Has the medicine you need
osteoporosis caused by
www.wardblacklaw.com

Ad:

© 1999-2007 Spine-health.com.

The information in Spine-health.com is not intended as a substitute for medical professional help or advice but is to be used only as an aid in understanding back pain and neck pain. See [Terms and Conditions](#), [Privacy Policy](#), [Sponsor Policy](#), and [Advertising Info](#).

Diagnosis of osteoporosis

- Differential diagnosis
 - Physical findings
 - Radiographic findings
 - Laboratory tests
 - Indications for bone density
 - Biochemical markers
 - Secondary osteoporosis
 - Clinic Worksheet (*pdf file*)
-

Differential diagnosis

Remember that not all fractures are osteoporotic. The differential diagnosis of fractures includes:

- Trauma
- Pathologic fracture from neoplasm
- Osteomalacia
- Paget's disease
- Infections (such as tuberculosis)
- Fibrous dysplasia
- Peripheral neuropathy
- "March" fractures from repetitive stress

☐ Many of these may be diagnosed from radiographs, bone scans, or magnetic resonance imaging studies. Sometimes bone biopsies are necessary.

Physical findings

Patients with decreased bone density usually have no specific abnormal physical findings. Those with vertebral compression fractures will have kyphosis, protruding abdomen and height loss. Back tenderness is usually only present after an acute fracture. Gait speed and grip strength are often reduced in patients who have or are about to have a hip fracture. Visual acuity should be checked in geriatric patients because it is a risk factor for falling.

Secondary causes of osteoporosis may be associated with physical findings, such as nodular thyroid, hepatic enlargement, cushingoid features, skin rashes, jaundice, abnormal dentition, and findings of hypogonadism.

Xray findings

Sometimes decreased bone density ("demineralization") can be detected by xray, but bones can appear normal despite loss of 30% of bone mineral. On the other hand, bones in over-exposed films can appear demineralized when they aren't. Bone density measurements are much more accurate than xrays in determining bone density.

The "Singh index" of the proximal femur correlates with bone density. The trabeculae of the femur are lost in sequence, depending on the physical stresses to the bone, so the remaining trabecular pattern indicates the severity of bone loss.

Fractures are discussed in the clinical description page.

Laboratory tests

These costs are several years old and need updating

Test	Charge
Chemistry panel	\$57
Serum calcium	\$22
24hr urine calcium	\$22
Serum phosphate	20
Creatinine	\$18
Magnesium	\$25
Alkaline phosphatase	\$22
CBC	\$21
TSH	\$43
Testosterone	\$61
25OH vitamin D	\$61
PTH, intact	\$94
N-telopeptide	\$49
Bone-specific alk.phos.	\$??
Protein electrophoresis	\$??

For an uncomplicated patient with osteoporosis, a lab workup would be a chemistry panel, CBC, phosphate, TSH and 24-hour urine calcium. Males should have testosterone measured. The main purpose of laboratory tests is to check for secondary causes of osteoporosis such as cases of renal or hepatic failure, anemia, acidosis, hypercalciuria, and abnormalities of calcium/phosphate. A nice paper by Tannenbaum, C. documents the utility of these kind of blood tests.

Alkaline phosphatase is an inexpensive method of checking for osteoblastic activity. ~~It is~~ not as sensitive or specific as newer "bone markers" but it will detect moderate to severe osteomalacia or Paget's disease.

The 24-hour urine calcium measurement is frequently ignored but it is a valuable and inexpensive test. High levels are seen in idiopathic hypercalciuria, and low levels suggest malabsorption. The test should be done on a patient's customary calcium intake.

Protein electrophoresis should be done whenever a patient presents with new fractures. Both serum and urine tests should be done because some patients with myeloma have abnormalities in only one.

Corticosteroid excess that causes osteoporosis can usually be detected clinically by Cushingoid features. A urine cortisol can be helpful in puzzling cases.

Gonadal hormones are very important causes of osteoporosis. In females who are postmenopausal, it is not helpful to measure levels of estrogens or gonadotropins. In males, however, testosterone levels should be measured because there is much greater variability in the prevalence of hypogonadism. Also, men may have low testosterone without other clinical symptoms. If testosterone is low, then further work-up is needed.

Vitamin D and parathyroid hormone levels are expensive tests. Some physicians order them routinely, but the expense does not seem justified. Mild vitamin D deficiency frequently occurs in the absence of hypocalcemia, but if vitamin D supplementation is routinely given, it is not necessary to perform this test in patients with normal calcium. Primary hyperparathyroidism nearly always causes hypercalcemia. Secondary hyperparathyroidism may occur with normal calcium, but most of these cases will be detected by low urine calcium or decreased renal function. In patients with abnormal serum calcium or with unusually severe bone disease, however, the 25-OH-vitamin D and parathyroid hormone levels should be measured.

The 25 OH-vitamin D is more useful than the 1,25 (OH)₂ vitamin D level. In fact, there are VERY FEW reasons to ever measure the 1,25(OH)₂ vitamin D levels! If your patient needs this test, you probably should refer him or her to a specialist. Check out this page about vitamin D levels .

Bone specific biochemical markers are discussed on the next page.

Indications for bone density measurements

Over the last decade there have been many debates about screening bone density. Several organizations have performed detailed cost-benefit studies and developed guidelines; these must be continually revised as new findings about treatment effects are discovered (U.S. Preventive services Task Force, American Association of Clinical Endocrinologists, National Osteoporosis Foundation). Bone density tests carry no physical risks, but there is a problem of over-interpretation of results, so that healthy ordinary average people think they are at a much higher risk than they actually are. In 2000 an NIH consensus conference concluded: "Until there is good evidence to support the cost-effectiveness of routine screening, or the efficacy of early initiation of preventive drugs, an individualized approach is recommended."

This is my personal list, following the principle that a physician should order a test only if he or she plans to change therapy as a result:

Patients with risk factors or conditions that cause osteoporosis

- Postmenopausal woman with family history of hip fractures or kyphosis
Medications: corticosteroids, dilantin, gonadotropin releasing hormone agonists, loop diuretics, methotrexate, thyroid, heparin, cyclosporin, depot-medroxyprogesterone acetate
- Hereditary skeletal diseases: osteogenesis imperfecta, rickets, hypophosphatasia
- Endocrine and metabolic: hypogonadism, hyperparathyroidism, hyperthyroidism,
- Cushing syndrome, acidosis, Gaucher's disease
- Anorexia
- Malabsorption
- Cystic fibrosis
- Marrow diseases: myeloma, mastocytosis, thalassemia
- Renal insufficiency
- Hypercalciuria
- Hepatic disease
- Depression
- Spinal cord injury
- Systemic Lupus
- Weight below healthy range
- Cigarette smoking

Post-menopausal women

Women within ten years of menopause may decide to take estrogens if their bone density is low, especially since estrogen seems to be most effective at preventing hip fractures when started close to menopause. Women over age 65 could still have osteoporosis without other risk factors, and in that case medications would be beneficial.

Young patients with a non-traumatic fracture

For example, if a patient suffered a fracture from uncertain trauma, the measurement can be used to "rule out" osteoporosis as a cause. If the bone density shows strong bone (WHO category of normal), then a bone scan should be done to check for pathologic lesions or malignancy

"Demineralization" on an xray in young patients

Standard radiographs are not very accurate methods of detecting change in bone mineral. Demineralization on a routine xray may be the first sign of osteoporosis, or it may represent an over-exposed film. This indication is more appropriate in a young person, since all elderly people have some degree of bone loss.

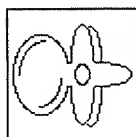
Baseline evaluation for patient with fragility fracture

Patients with vertebral compression fractures or hip fractures should usually have a baseline bone density measurement to help evaluate subsequent therapy. This is not as straightforward as it first appears, however. Some therapies that significantly reduce fractures may not cause significant improvement in bone density when measured in an individual patient. More studies are needed to provide evidence that follow-up bone density examinations are really helpful. Physicians must also be aware of the reproducibility of the density machines.

In elderly women with established osteoporosis, it is reasonable to start therapy without getting a bone density. It is unlikely that important future therapies will depend on knowing the bone density. In younger women, however, new therapies may be developed a decade from now, and it may be helpful to know the bone density response to treatment available now.

REFERENCES

Updated 1/20/04



**Osteoporosis and
Bone Physiology**

Home Page

Next page

EXHIBIT B



Endocrine Disorders &
Endocrine Surgery

site search

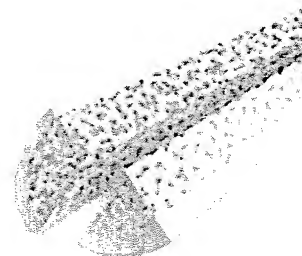
Osteoporosis

Making the Diagnosis of Osteoporosis

Definition of Osteoporosis

Osteoporosis is a condition of decreased bone mass.

This leads to fragile bones which are at an increased risk for fractures. In fact, it will take much less stress to an osteoporotic bone to cause it to fracture. The term "porosis" means spongy, which describes the appearance of osteoporosis bones when they are broken in half and the inside is examined. Normal bone marrow has small holes within it, but a bone with osteoporosis will have much larger holes. This picture shows a bone with osteoporosis on the top with large spongy holes, and a normal bone on the top with normal small passageways. In severe osteoporosis, this can be exaggerated much more than shown here!



Diagnosing Osteoporosis

There is no method of determining the actual **structure** of bones without actually removing a piece during a biopsy (which is not practical or necessary). Instead, the diagnosis of osteoporosis is based on special x-ray methods called **densitometry**. Densitometry will give accurate and precise measurements of the amount of bone (not their actual quality). This measurement is termed "bone mineral density" or BMD.

► The World Health Organization "WHO" has established criteria for making the diagnosis of osteoporosis, as well as determining levels which predict higher chances of fractures. These criteria are based on comparing bone mineral density (BMD) in a particular patient with those of a 25 year old female. BMD values which fall well below the average for the 25 year old female (stated statistically as 2.5 standard deviations below the average) are diagnosed as "osteoporotic". If a patient has a BMD value less than the normal 25 year old female, but not 2.5 standard deviations below the average, the bone is said to be "osteopenic" (osteopenic means decreased bone mineral density, but not as severe as osteoporosis). Interestingly, although these criteria are widely used, they were devised in a Caucasian female so there will be some differences when these levels are applied to non Caucasian females or to males in general. Despite this flaw, measurement of BMD is used daily and has proven to be very helpful in all groups. Some men will be subject to increased fracture rates when they have significantly less BMD than the predicted fracture level for women. In other words, some men will be at increased risk for fracture even when they have osteopenia.

Osteoporosis is different from most other diseases or common illnesses in that there is no one single cause. The overall health of a person's bones is a function of many things ranging from how well the bones were formed as a youth, to the level of exercise the bones have seen over the years. During the first 20 years of life, the formation of bone is the most important factor, but after that point it is the prevention of bone loss which becomes most important. Anything which leads to decreased formation of bone early in life, or loss of bone structure later in life will lead to osteoporosis and fragile bones which are subject to fracture. Several more pages go into these topics in more detail.



Citracal



[Diagnosing Osteoporosis](#) | [Normal Bone Formation](#) | [Maintenance of Strong Bones](#) | [Exercise & Osteoporosis](#)
[Calcium and Osteoporosis](#) | [Menopause and Osteoporosis](#) | [Prevention & Treatment](#) | [Hyperparathyroidism](#)
[Calcium Treatments](#) | [Estrogen Treatments](#) | [New Drug Treatments](#)

[Osteoporosis Home Page](#) | [Endocrine Web Home Page](#)

| [Search Endocrine Web](#) | [Site Map of EndocrineWeb](#) |

Copyright © 1997-2002. Endocrine Web and the Norman Endocrine Surgery Clinic. All rights reserved.

Disclaimer

EXHIBIT C

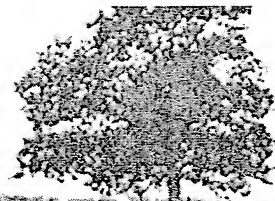
Advertisement

Diagnosed with
METASTATIC BREAST CANCER

learn more about
chemotherapy



imaginis
THE WOMEN'S HEALTH RESOURCE



[HOME](#) [ABOUT US](#) [DISCUSSIONS](#) [FREE NEWSLETTER](#) [NEWS](#)

Search

search tips

☒ Breast Cancer Topics

☐ Related Cancer Topics

☐ Key Topics

☐ Imaginis Partners

☐ Sponsors

☐ Awards

☐ Professional Resources

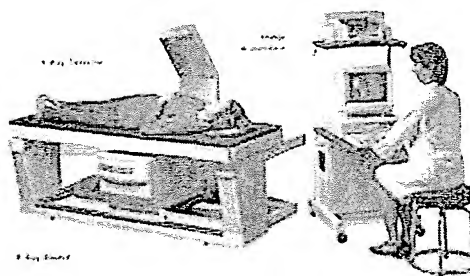
Women's Health

Osteoporosis

Diagnosis of Osteoporosis with Bone Mineral Density Measurement

For

Technologists often diagnose osteoporosis by measuring a patient's bone mineral density (BMD). Bone mineral density measures the amount of calcium in specific bones. Most methods for measuring BMD (also called bone densitometry) are non-invasive, painless and available on an outpatient basis. Bone densitometry can also be used to estimate a patient's risk of fracture. BMD methods involve taking energy x-rays (DEXA) or CT scans (Osteo CT or QCT) of bones in the spinal wrist, arm or leg. These methods compare the numerical density of the bone (calculated from the image), with empirical (historical) data bases of bone density to determine whether a patient has osteoporosis, and often, to what degree.



A patient receives a DEXA bone densitometry exam (image courtesy: Hologic)

Main Menu:

- Overview
- Types of Bone Mineral Density Tests
- Guidelines for Bone Mineral Density Testing
- Understanding the Results of Bone Mineral Tests

Overview

Advertisement

Diagnosed with
**METASTATIC
BREAST
CANCER**

Learn more
about a
chemotherapy
option ▶

DEXA (Dual Energy X-ray Absorptiometry) is the most widely available method of bone densitometry, and most insurance plans will cover the cost for the test, given certain medical indicators are present. Bone mineral density measurement is painless, and requires no injections, invasive procedures, sedation, special diet, or any other advance preparation. During a DEXA exam, the patient lies fully clothed on a padded table while the system scans one or more areas of bone (usually the spine or hip). The entire exam typically takes just a few minutes to complete. DEXA uses x-rays, the radiation dose is less than during a chest x-ray. Each bone density is plotted against the "normal" for a healthy young adult or against age-matched control data. A radiologist or other physician then interprets the data and creates a concise report on the status of the patient's bone density.

Laboratory tests that measure the amount of collagen in urine samples can indicate bone loss. Lab tests may also be used in conjunction with DEXA or other methods of bone densitometry to diagnose osteoporosis.



A woman sits while receiving ultrasound bone densitometry by measurement of her heel.

New methods of measuring osteoporosis using ultrasound have also been developed. One such ultrasound system measures BMD at the patient's heel and takes about one minute. The ultrasound systems for testing osteoporosis are smaller and less expensive than traditional DEXA. These systems have recently received US Food and Drug Administration (FDA) clearance. The hope is that this compact, lower cost system will allow this vital diagnostic test to become more widely available in the future. However, peripheral sites such as the heel measured by ultrasound densitometry may not be as sensitive as techniques such as DEXA or QCT that measure the

hip or spine since the heel may be normal in bone density even when central sites such as the hip or spine are already significantly abnormal.

Further, density changes in the heel occur much slower than in the hip or spine. Therefore ultrasound densitometry should not be used to monitor a patient's response to therapy. However, the new ultrasound densitometry systems will allow many people access to bone densitometry and potentially diagnose osteoporosis before a traumatic fracture occurs.

Summary of Types of Bone Mineral Density Tests

- Ultrasound measures the heel
- DEXA (Dual Energy X-ray Absorptiometry) measures the spine, hip or total body
- SXA (single Energy X-ray Absorptiometry) measures the wrist or heel
- PDXA (Peripheral Dual Energy X-ray Absorptiometry) measures the wrist or finger
- RA (Radiographic Absorptiometry) uses an X-ray of the hand and a sand wedge to calculate bone density
- DPA (Dual Photon Absorptiometry) measures the spine, hip or total body
- SPA (Single Photon Absorptiometry) measures the wrist
- QCT (Quantitative Computed Tomography) measures spine or hip

The accuracy of bone mineral density test is high, ranging from 85% to 99%. According to physicians, QCT is the most accurate BMD test and ultrasound is the least accurate of the tests. DEXA is the most widely available BMD test and its accuracy is in between those of QCT and ultrasound. However, QCT is not as widely available and delivers more radiation to the patient than DEXA.

CO

11

[Return to Osteoporosis Main Menu](#)

Advertisement

*Have you given your
doctor the full story of
your Migraines?*

TOPAMAX[®]
(topiramate)
Click to view
important safety
information

**WATCH THIS
VIDEO**


[Click Here to Recommend This Article To A Friend](#)

[Home](#) | [About Us](#) | [Discussions](#) | [Free Newsletter](#) | [News](#) | [Advertise With Us](#) | [Format For Printing](#) | [5](#)

Imaginis.com subscribes to the HONcode principles of the Health on the Net Foundation.

Copyright © 1997-2007 Imaginis Corporation. All rights reserved. Imaginis® is a registered service mark Imaginis Corporation, a health services company. All other trademarks and copyrights are property of the respective owners. Note: Use of this online service is subject to the disclaimer and the terms and conditions contained herein. Information found within the Imaginis.com website or in other sites linked to from Imaginis.com is provided for educational purposes only and is not intended to be used as a substitute for diagnosis and treatment by a medical doctor. Imaginis does not endorse and has no responsibility for the other sites listed on Imaginis.com, and provides links and references merely as a convenience to its user immediate medical attention if your condition is urgent.

EXHIBIT D

 [Print this Page for Your Records](#)[Close Window](#)

Session: Osteoporosis Treatment (Preclinical) I
Presentation Number: 1011
Title: A Bisphosphonate Analog that Lacks Anti-Remodeling Activity Prevents Osteocyte and Osteoblast Apoptosis In Vivo
Presentation Start: 9/17/2007 11:00:00 AM
Presentation End: 9/17/2007 11:15:00 AM
Category: L - Osteoporosis - Treatment (preclinical)
Authors/Speakers: L. J. Plotkin, J. Goellner, K. Vyas*, R. S. Shelton*, R. A. Wynne*, R. S. Weinstein, S. C. Manolagas, T. Bellido. Center for Osteoporosis and Metabolic Bone Diseases, Univ Arkansas for Medical Sciences and Central Arkansas Veterans Healthcare System, Little Rock, AR, USA.

A major effect of bisphosphonates (BPs) on bone is inhibition of resorption resulting from their ability to induce osteoclast death or interfere with osteoclast function. Nonetheless, BPs also prevent osteocyte and osteoblast apoptosis *in vitro* and *in vivo*, but the contribution of the latter property to the overall beneficial skeletal effects of these agents remains unknown. We compared herein the effect of IG9402, a BP analog that preserves osteoblast and osteocyte viability but does not induce osteoclast apoptosis *in vitro*, with that of alendronate, a classic BP that affects osteoclasts as well as osteoblasts and osteocytes. Swiss Webster mice (7-8 per group) were implanted with placebo or prednisolone (GC) pellets (2.1 mg/kg/d) for 10 days, and were injected daily with saline or 2.3 $\mu\text{mol/kg/d}$ alendronate or IG9402, starting 3 days prior to pellet implantation. Alendronate decreased the serum levels of C-telopeptide and osteocalcin, markers of bone resorption and formation, respectively, as well as the levels of osteocalcin and collagen1A1 mRNA in vertebral bone. On the other hand, IG9402 did not affect serum levels of C-telopeptide or osteocalcin nor bone mRNA levels of osteocalcin or collagen1A1. Moreover, whereas alendronate decreased cancellous bone formation rate from 0.43 ± 0.25 to $0.09 \pm 0.03 \mu\text{m}^2/\mu\text{m/d}$ ($p < 0.05$), IG9402 did not affect it significantly ($0.39 \pm 0.04 \mu\text{m}^2/\mu\text{m/d}$). These findings are consistent with a decrease in bone remodeling resulting from inhibition of resorption by alendronate but not by IG9402. Furthermore, the increase in osteoblast and osteocyte apoptosis induced by GC (from 5.6 ± 2.5 to $15.1 \pm 6.0\%$ and 3.1 ± 1.7 to $7.1 \pm 1.1\%$, respectively, $p < 0.05$) was prevented not only by alendronate, as previously shown, but also by IG9402. In addition, GC induced a significant decrease in the load required to break the 6th lumbar vertebra (68.1 ± 11.6 to 47.1 ± 8.5 N, $p = 0.006$) and a decrease that was non-significant in the compression stress (27.8 ± 5.3 to 21.2 ± 4.9 in MPa $p = 0.095$); and both alendronate and IG9402 prevented the decreased ability of the vertebrae to sustain load induced by GC. We conclude that preservation of osteoblast and osteocyte apoptosis by bisphosphonates is an important, but heretofore unappreciated, mechanism of the beneficial effect of these drugs on bone. Preservation of bone strength without inducing osteoclast apoptosis by IG9402 opens new possibilities for the treatment of bone fragility in conditions in which a decrease in bone remodeling is undesirable.

OASIS - Online Abstract Submission and Invitation System™ ©1996-2007, Coe-Truman Technologies, Inc.